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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/614,037	07/08/2003	Manfred Reiter	14693-0195	9074

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EXAMINER	
VOGEL, NANCY TREPTOW	
ART UNIT	PAPER NUMBER
1636	
MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/614,037	REITER ET AL.	
	Examiner	Art Unit	
	NANCY VOGEL	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 April 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *34-36 and 46-66* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *34-46, 46-66* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 34-36 and 46-66 are pending in the case.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 49, 52, 60 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This rejection is maintained essentially for the reasons made of record in the previous Office action, mailed 1/28/08.

The specification as originally filed does not provide support for the invention as now claimed: "wherein the infected cells are incubated in an animal protein free culture medium comprising at least one hydrolysate selected from the group consisting of a soy hydrolysate and a yeast hydrolysate" (49), and "where the virus is propagated in an animal protein free culture medium comprising at least one hydrolysate selected from the group consisting of a soy hydrolysate and a yeast hydrolysate" (52), "wherein the infected culture of cells are cultivated in an animal protein free culture medium comprising at least one hydrolysate selected from the group consisting of a soy

hydrolysate and a yeast hydrolysate" (6), since the specification discloses only the growth medium comprising both yeast and soy hydrolysate. This a new matter rejection. The specification does not provide sufficient blazemarks nor direction for the instant methods encompassing the above-mentioned limitations, as currently recited. The instant claims now recite limitations which were not clearly disclosed in the specification as-filed, and now change the scope of the instant disclosure as-filed. Such limitations recited in the present claims, which did not appear in the specification, as filed, introduce new concepts and violate the description requirement of the first paragraph of 35 U.S.C. 112.

Applicants' arguments filed 4/22/08 have been considered but have not been found convincing. Applicants have pointed to sections in the specification for support, but these sections do not disclose the claimed method in which only one of the hydrolysates selected from soy or yeast hydrolysate are utilized. It is clear from the first paragraph, in fact, that animal product free media containing both yeast and soy hydrolysates are intended and supported. The amendment to the claims in which the language "at least one" does not change the meaning of the claims. Therefore the rejection is maintained.

Claims 34-36, 46-66 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to

which it pertains, or with which it is most nearly connected, to make and/or use the invention.

This rejection is maintained essentially for the reasons set forth in the previous Office action, mailed1/28/08.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The nature of the invention: The invention is drawn to a method of producing immunogenic composition comprising a virus or a virus antigen, comprising growing cultures of cells in an animal protein free medium comprising soy hydrolysate and yeast hydrolysate.

The state of the prior art: The prior art disclosed methods of cell culture comprising soy and yeast hydrolysate, and also generally include the addition yeast and/or soy hydrolysates, and in some disclosures, animal protein components, either in the form of undefined serum additives, or particular animal proteins in defined form. Cell culture techniques generally are the result of trial and error experimentation.

The level of predictability in the art: The prior art in methods of cell culture and media appropriate for cell growth is unpredictable, and appears to be a matter of trial

and error experimentation. Shibuya et al. (US Patent 6,406,909) disclose a method of growth of cells in basal media comprising soy and yeast hydrolysates that meet the limitations of the claims; however, as acknowledged by applicant in the response of 1/31/07, Shibuya et al. disclose that growth of the cells required the addition of a protein which is recombinantly-produced insulin (page 8-9). Therefore, Shibuya et al. discloses the exact conditions disclosed by applicant, and yet, cell growth or maintenance was not supported under those conditions. Therefore, it is clear that the field is unpredictable, and that it cannot be predicted whether any particular type of culture media, will successfully support the growth of any cell type as claimed by applicant.

Breadth of the claims: The claims are very broad, since some are drawn to a method of cell producing any immunogenic composition comprising any virus or any virus antigen, using any cell type, grown with any "animal protein free medium", with the only proviso being that soy and yeast hydrolysate are present in certain concentrations and have components with a molecule weight of less than 100 Daltons.

Amount of guidance: The amount of guidance provided is small, since it is only stated in the specification that any "basal" medium may be used.

Existence of working examples: The specification discloses VERO cells, grown with one type of medium, i.e. basal DMEM/HAM's F12(1:1) medium supplemented with "inorganic salts, amino acids, vitamins and other components", in addition to "sodium bicarbonate…L-Glutamine" and soy and yeast hydrolysates (page 17).

Quantity of experimentation: In the absence of appropriate guidance for the full scope of the claims, and the unpredictability in the art, the quantity of experimentation needed to practice the invention as claimed would be extensive, since one would have to use trial and error experimentation to determine the type of cell culture needed to culture any particular cell type. It remains possible that the claimed methods would not support culture of some cell types, as evidenced by Shibuya et al. No guidance regarding this matter is disclosed in the specification.

Applicant's arguments filed 4/22/08 have been considered but have not been found convincing. Applicants have argued that one skilled in the art would be able to follow the recited steps to practice the claimed invention in view of the specification and based own what is known in the art without any undue experimentation, and point to examples in the specification at paragraphs 53 to 70 for enablement. However, it is maintained, as was discussed above in the statement of the rejection, that there is evidence in the prior art that the art of cell culture was unpredictable, and that the determination of cell culture conditions which would result in the successful culture of any particular cell type cannot be predicted and must be determined using experimentation which may be quite extensive and unpredictable. The determination of which possible components, which are virtually infinite in number, which , when added to a culture medium, would result in cell maintenance and growth, is not routine and predictable. Therefore the rejection is maintained.

Claim Rejections - 35 USC § 103

Claims 34-36 and 46-66, are rejected under 35 U.S.C. 103(a) as being unpatentable over Price et al. (WO 98/15614) in view of Kistner et al. (US Patent 5,753,489), Luderer et al. (US P patent 4282315), Gauri et la. (US Patent 4,322,404) and Quest International Product Information, Norwich NY, 1995, and Sheffield Pharma Ingredients, Cell Nutrition, Hydrolyzed Proteins & Yeast Extracts, Technical Manual (all previously cited).

This rejection is maintained for the reasons made of record in the previous office action, 1/28/08.

Price et al. disclose a method of culturing cells comprising providing a culture of cells that have been grown in an animal protein free medium comprising soy hydrolysate at a concentration of about .1% and/or yeast hydrolysate at a concentration of0.1% to about .8% (pages 19-20) . Price et al. disclose this method is useful for culture of animal cells including human cells and kidney cells (see page 24). Price disclose the method may be used to grow and produce viruses using cell culture (page 2).

The difference between the reference and the instant claims is that the steps of infecting the cells with virus, incubating the infected cells to propagate the virus, harvesting the virus and preparing an immunogenic composition, and specifically, conducting those steps using particular viruses, is not disclosed. Furthermore, purifying said virus or antigen by ion exchange or gel filtrations is not disclosed Furthermore, particular sizes of the molecules in the hydrolysates, i.e. 90% of the molecules in the

hydrolysates have a molecule weight of less than or equal to 1000 Daltons, is not disclosed.

However, Kistner et al. disclose a method of producing an immunogenic composition comprising virus or virus antigen, comprising providing a culture of a mammalian cells, infecting the cells with a virus, incubating the culture of cells to propagate the virus, harvesting the virus or antigen, and preparing an immunogenic composition from the virus or antigen (see col. 5-6). The virus may be orthomyxoviridae, paramyxoviridae and reoviridae, and the cells may be vertebrate cells such as VERO, CV-1, LLC-MK2, MDCK, MDBK cells (col. 6, lines 1-15). Luderer et al. and Gauri et al. disclose the purification of virus by such well known techniques as gel filtration (col. 2 line 55-70 of Luderer et al.; see col. 3, lines 5-15 of Gauri et al.). Quest International Product Information discloses that HY-SOY, which is a well known soy hydrolysate, has 25.4% of molecules less than 200 D, 57.5% in the 200-500 D range, and 16.8% in the 500-1000 D range. The product pages disclose that the hydrolysates are useful for applications that require high solubility, including microbiological laboratories and in fermentation products requiring a water soluble, vegetable source peptone.. . Furthermore, technical literature from Sheffield Pharma, current makers of such products as “Hy-Soy”™ and “Hy-Yest” ™ also show that the molecular weight distribution of virtually all products is: 90% of molecules are less than 1 kD in size.

It would have been obvious to one of ordinary skill in the art to have included the steps of infecting the cultured cells with a virus of interest, cultivating the infected cells, harvesting the virus, and isolating an immunogenic antigen therefore, as disclosed by

Kistner et al., in the method of cultivating cells disclosed by Price et al., since both references disclose the growth of cells in culture for the purpose of producing virus or recombinant products of interest. It would have been further obvious to use well known soy or yeast hydrolysates commercially available, such as those disclosed in the Quest International Product Information pages, which are disclosed to be "refined" and to have a molecule weight distribution in which at least 90% of the molecules have a molecule weight of less than or equal to 1000 Daltons. Furthermore, technical literature from Sheffield Pharma, current makers of such products as "Hy-Soy"™ and "Hy-Yest" ™ also show that the molecular weight distribution of virtually all products is: 90% of molecules are less than 1 kD in size. One would have been motivated to do so by the disclosure of Price et al. that the method avoids contamination by animal proteins, and the usefulness of the cell culture method for producing virus, and the disclosure of the Quest International product information, which discloses that the hydrolysates are refined and are of low molecular weight, and are useful for applications that require high solubility, including microbiological laboratories and in fermentation products requiring a water soluble, vegetable source peptone.. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Applicants' arguments filed 4/22/08 have been considered but have not been found convincing. Applicants argues that the claimed method required animal protein

free medium, and not the replacement or substitution of animal-derived products (page 9 of the arguments). However, it is maintained that the wording of the reference, in which it is stated that "the present invention also relates to methods for replacing or substituting animal-derived products with plant peptides, plant lipids, plant fatty acids, and/or enzymatic digests or extracts of yeast cells (or combinations thereof)" is not particularly relevant. The result is still a culture medium in which animal products are not used, but yeast and/or soy hydrolysates are used. Whether one describes this as a "substitution" for animal products, or simply a medium comprising these products, does not change the nature of the method and the culture medium. Therefore, the rejection is maintained. (It is noted that applicants mistakenly stated that claims 34-36 and 46-48 were rejected; claims 34-36 and 46-66 were included in the rejection in the action of 1/28/08 and are included in the instant rejection).

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to NANCY VOGEL whose telephone number is (571)272-0780. The examiner can normally be reached on 7:00 - 3:30, Monday - Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/NANCY VOGEL/
Primary Examiner, Art Unit 1636

NV
8/16/08